

# Common Variable Immunodeficiency (CVID) and Autoimmunity

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## Abstract

Autoimmunity is observed by almost one-third of patients with CVID. Different mechanisms including genetic defects and dysregulation of innate and adaptive immunity leads to autoimmunity in these patients CVID. The clinical phenotypes of autoimmunity in CVID patients comprise fall in a wide spectrum, from organ-specific autoimmunity to systemic complications. The most common autoimmunity is autoimmune cytopenia in CVID patients. In this article, we have provided a collection of the most significant and recent information about prevalence, genetics, pathogenesis and clinical manifestations of autoimmunity in CVID patients, and provided an overview on its management and future perspective.

**Keywords:** common variable immunodeficiency, autoimmunity, autoimmune cytopenia, adaptive immunity

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## Introduction

CVID is a heterogeneous group of primary immune deficiencies (PIDs) that is considered as the most common symptomatic PID (1). It is characterized by a reduction in two major serum immunoglobulin isotypes, usually IgG and IgM and/or IgA along with diminished or lack of antibody production (2). The incidence of CVID is

estimated to be between 1:25,000 to 1:50,000 and its prevalence is rather equal in males and females (3). Although most PIDs are detected in the early years, CVID patients are often diagnosed in the third or fourth decade of life. The majority of patients (70% - 80%) suffer from sinopulmonary infections and others (30% -50%) have more non-infectious complications includ-

ing gastrointestinal ailments, inflammatory/ autoimmune diseases, lymphoproliferative disorders, allergic symptoms and malignancies (4). Despite the improvements in mortality rate of CVID due to extensive usage of IgG replacement therapy, which can reduce severe infections such as pneumonia and sepsis, non-infectious complications-dependent mortality and morbidity are still a grave concern for these patients (5, 6).

Autoimmune manifestations are estimated to affect approximately 30% of all CVID patients (7). Idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA) and autoimmune neutropenia are respectively the most prevalent autoimmune disorders found in CVID patients. However, autoimmunity can engage other tissues such as gastrointestinal tract, lungs and skin. In this article, we have provided a collection of the most significant and recent information about prevalence, genetics, pathogenesis and clinical manifestations of autoimmunity in CVID patients, and presented an overview on its management and future perspective.

### Prevalence of Autoimmunity in CVID

It has been estimated that autoimmunity affects approximately 21-37% of CVID patients. In 1999, Cunningham-Rundles et al. reported a large cohort about CVID and demonstrated that the prevalence of autoimmunity was 21.6% and mostly hematologic including 6% ITP and 4.8% AIHA (5). In 2007, Quinti et al. reported 25.9% autoimmunity with a profound difference with other researches, as the most frequent manifestation was vitiligo (13.4%) and Sjögren's syndrome (8.9%) (8). One year later, Chapel et al. indicated that the prevalence of autoimmunity was 21.6%; including ITP, vitiligo, autoimmune thyroiditis, AIHA and autoimmune neutropenia(9). In the two studies, the prevalence of autoimmunity were 36.6% (10) and 28.6% (11) as ITP was a more frequent autoimmunity in both. ITP, vitiligo and autoimmune thyroiditis were

the most frequent autoimmune disorders in a study by Ramírez-Vargas et al. (12). Recently, Ho et al. investigated non-infectious complications in CVID patients in the united states and observed autoimmunity in 33.2% of the patients(13). They reported that there was no gender difference in the prevalence of autoimmunity and the clinical spectrum.

## 3. Pathogenesis of Autoimmunity in CVID

### 3.1. Genetic Defects

CVID is a phenotypically heterogeneous disease and various factors such as genetic defects and epigenetic changes are involved in the pathogenesis of this disease (14, 15). A family history has been found in approximately 20-25% CVID patients that reveals the role of genetics, but most cases were sporadic (3). Genetic impairments in the development of B and T cells, signaling pathway, and B cell class switch recombination as well as somatic hypermutation could be associated with breaking self-tolerance and manifestation of autoimmunity in CVID (16-18). Among the 12 monogenic mutations associated with CVID that are mentioned on the Online Mendelian Inheritance in Man (OMIM) database(19), we focus on those related to autoimmunity. Genetic defects associated with autoimmunity in CVID patients are presented in **Table 1**.

Defects in the transmembrane activator and calcium-modulating ligand interactor (TACI) (encoded by the TNFRSF13B gene) have been found in almost 8 to 10% of patients (20, 21). Defect in TACI causes autoimmune disorders and lymphoid hyperplasia because of the dysfunction of BCR, TLR-7 and TLR-9 and consequently missing the mechanism of self-tolerance (15, 22). Interestingly, autoantibody-mediated autoimmunity is more likely to be found in CVID patients who have heterozygous mutation in the TNFRSF13B variant compared with those with homozygous mutations, reflecting dominant negative or haploinsufficiency effect (23).

**Table.1.** Genetic defects associated with autoimmunity in CVID patients

Mutated genes	Function	Type of Affected cells	Name of monogenetic disorder
TACI	A receptor on B cells that binds to BAFF and APRIL	B and T cells	TNFRSF13B mutation/ Loss of function
LRBA	A molecule localized in the vesicles and endoplasmic reticulum for trafficking and protection of CTLA4	T cells	Aautosomal dominant/LOF
CTLA-4	an inhibitory checkpoint protein on activated T cells and regulatory T (Treg) cells and bind to CD28	T cells	Autosomal dominant/ LOF
STAT3	A transcription factor regulating cellular proliferation and differentiation especially in Th17	T cells and ILCs	Gain of function
PI3K $\delta$	A signaling enzyme downstream of T and B cell and other receptors	Most of immune cells	Gain of function
NF- $\kappa$ B1	transcriptional factors regulating diverse processes especially B cell differentiation and function and immune response to microbial and inflammatory stimuli	Most of immune cells	Autosomal dominant/LOF

CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) is recognized as an inhibitory T cell receptor, and LRBA (lipopolysaccharide-responsive beige-like anchor) is requisite for CTLA-4 cell surface expression and prevents lysosomal degradation. They are two connected proteins the defects of which can result in autoimmunity in CVID patients (24, 25). Clinically, patients with CVID phenotype suffer from autoimmunity, lymphoid hyperplasia and also severe inflammatory bowel disease (26-28). Autosomal dominant syndrome due to heterozygous CTLA4 mutations led to autoimmune cytopenia (62%), lung (68%) and gastrointestinal (59%) diseases in a large cohort study on CVID patients (29). In recent years, several studies have reported LRBA mutations in patients primarily diagnosed as CVID(30).

Mutations in some signaling pathways have been observed in CVID patients with autoimmunity (31). Phosphoinositide 3-kinase (PI3K), a

signaling molecule downstream of T and B cell receptors, TLR, and co-stimulatory and cytokine receptors are essential for the cell growth and survival of immune cells and for Th1 and Tfh cell differentiation (32). GOF mutation in PIK3CD gene encoding PI3K $\delta$  subunit has been seen in patients with CVID phenotype, nowadays called activated PI3K $\delta$  syndrome (APDS). Patients with APDS manifest some of non-infectious manifestations, including lymphoproliferation (75%), autoinflammatory disease (34%), and lymphoma (13%) (33-35). Another signaling molecule is NF- $\kappa$ B (Nuclear factor kappa-light-chain-enhancer of activated B cells) that includes 5 related proteins (36). This molecule is critical for diverse processes such as B cell differentiation and function, cytokine production by innate immune cells as well as other vital cell signaling pathways (37). Autosomal-dominant defects in

NF- $\kappa$ B1 lead to some non-infectious complications including autoimmunity, lymphoid hyperplasia, lung disease, liver disease, enteropathy, granulomas and malignancy in CVID patients (38, 39). Additionally, heterozygous NFKB2 mutations has been accompanied by an early onset of hypogammaglobulinemia and autoimmune endocrine abnormalities (40). Since NF- $\kappa$ B are activated by ICOS receptors, mutations in this receptor may also be responsible for the mentioned disorders (41). GOF mutations in STAT3 is thought to cause severe manifestations of autoimmune disease by promoting the activation and development of autoimmunity-associated TH17 subsets in CVID patients (42). Overall, these new monogenic defects share clinical phenotypes with CVID and they are considered as distinct entities that may occasionally be misdiagnosed as CVID.

### 3.2. Immunologic Defects

#### 3.2.1. Defects in adaptive immunity

Abnormalities have been previously demonstrated in a number of immune cells especially in lymphocyte subpopulations in CVID patients (43, 44). CVID patients have defective development of class switched memory B cell (CD19+ CD27+ IgD-) (45), hence reduced proportion of total switched memory B cells (46). This reduction has been reported to be associated with certain clinical features like splenomegaly, granulomatous disease, lymphadenopathy and autoimmune cytopenia (47). Moreover, it has been shown that reduced switched memory B cell percentage strongly correlates with autoimmunity in patients with CVID compared to serum IgG levels (48). Indeed, patients with reduced numbers of switched memory B cells showed increased risk of autoimmune cytopenia and systemic autoimmune disease (49).

Another important B cell subset for CVID patients is CD21<sup>low</sup>. The number of circulating CD21<sup>low</sup> B cell increases in CVID patients with autoimmune disease, suggesting an association with autoimmunity (50, 51). Boileau et al. reported a correlation between the increased proportion of CD21<sup>low</sup> B cells and CVID associated with autoimmune cytopenia, but this association was not seen with other autoimmune diseases or splenomegaly (45). Also, Warnatz et al. pointed out an increase in CD21<sup>low</sup> B cell of CVID patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (52). Furthermore, Rakhmanov et al. reported that CD21<sup>low</sup> B cells produce more IgM than naïve B cells after stimulation with CD40L and IL2 (53) and CVID patients with autoimmunity showed higher levels of IgM compared with non-immune phenotypes (54), suggesting a pathogenic role for them as IgM may be involved in autoimmune cytopenia(55).

Activation-induced cytidine deaminase (AID) gene expression in CVID patient lymphocytes have been reported to be higher than healthy controls. When CVID patients were categorized according to AID protein expression, those with higher levels of AID showed greater numbers of B cells, elevated levels of IgA and increased incidence of autoimmune disease including ITP and AIHA (54). It suggests that elevated levels of AID may play a role in dysregulation of immune system and ultimately in the development of autoimmunity. Overexpression of B cell activating factor (BAFF), which promotes maturation and survival of B cells, has long been related to autoimmunity (56-60). However, Knight et al. have not observed an association between elevated BAFF levels and autoimmunity in CVID (61). Further studies are needed to refine the complex

relationship between BAFF and autoimmunity in CVID.

Some CVID patients with autoimmunity demonstrate disturbed T cell homeostasis (44). It has been indicated that CVID patients with autoimmunity had lower total T cells compared to those without autoimmunity (62). Bateman et al. found that autoimmunity in CVID is associated with lower naïve CD8<sup>+</sup> T cells and increased terminal differentiated CD8<sup>+</sup> T cells, suggesting a hyperactivated T cell phenotype (63). Furthermore, some studies showed reduced CD4<sup>+</sup> cells in CVID (64, 65). The most significant reduction in CD4<sup>+</sup> T cells was found in those with autoimmune cytopenia and organ specific autoimmunity (63, 66, 67). Within CD4<sup>+</sup> T cells, lower number of regulatory T cells was particularly associated with autoimmunity in CVID (66, 68). Genre et al. reported reduced levels of transcription factor forkhead box P3 (FOXP3) in CVID patients with autoimmunity compared to those without it (66). Moreover, dysfunction in suppressive activity of regulatory T cells has also been demonstrated in CVID patients with autoimmunity (69). In addition to the loss of naïve and regulatory T cells, Crotty et al. reported an increase in T helper type 1 (TH1) and follicular T helper (TFH) in association with autoimmunity in CVID (70). These findings demonstrate the association of defective B and T cell with autoimmunity.

### 3.2.2. Defects in innate immunity

Numerous immune defects and dysregulations including innate and adaptive have been detected in CVID patients with autoimmune disorders. It has been demonstrated that differentiation, maturation and function of DCs could be defective in some groups of CVID patients (71). These defects could contribute to breaking self-tolerance and the onset of autoimmune impairments in CVID patients. Additionally, the expression of co-stimulatory molecules such as CD80, CD86 and HLADR are diminished in

these patients (72-74). Chronic upregulation of interferon responsive genes has been reported in patients with inflammatory and autoimmune complications compared with those without it (75). Increased levels of soluble CD30 and CD26 can deviate the immune responses toward Th1, which intensifies autoimmunity condition (76). Increased IL-12 production by CD14<sup>+</sup> monocytes also makes such similar situation (77). Low MBL production, a critical component of innate immunity, facilitates the development of autoimmune disease in CVID (78). In CVID patients with inflammatory conditions, the number of innate lymphoid cells (ILCs) with inflammatory phenotype has significantly expanded in blood, and respiratory and gastrointestinal mucosa (79). Reactive oxygen species (ROS) generation has been remarkably increased by monocytes in CVID patients that may lead to some of non-infectious complications such as autoimmune disorders and pulmonary diseases (80). Interestingly, a connection has recently been found between autoimmunity and defective TLR7, TLR8, and TLR9 signaling (81). Defective signaling components in this pathway such as IRAK-4 and MYD88 may interfere with self-tolerance mechanisms and activate auto-reactive B cells which eventuate to SLE or RA (81, 82). It has been shown that cytokines play an important role in the pathogenesis of autoimmunity in CVID patients. Breakdown of peripheral tolerance by the activation of immature myeloid DCs (mDCs) due to escalated levels of IFN- $\alpha/\beta$  lead to activation of autoreactive B and T cells, and develop autoimmunity in these patients (7, 83).

## 4. Clinical Phenotypes and their managements in CVID patients with autoimmunity

In this section, we describe some autoimmune diseases along with their managements in CVID patients. The information of diseases, prevalence, diagnosis, treatments are provided in **Table 2**.

**Table.2.** Autoimmune diseases in CVID patients

AI disorders In CVID	Diseases	Prevalence	Diagnosis	Treatments
Hematologic disease	ITP	4%-20%	CBC and PBS Bone marrow biopsy	Immunosuppressive agents
	AIHA			IVIg
	Evans' syndrome autoimmune neutropenia			Monoclonal Abs
Gastrointestinal disease	IBD-like disease	10%-12%	Endoscopy with biopsy of the intestinal Liver enzymes	Immunosuppressive agents
	Autoimmune hepatitis			Monoclonal Abs
	Pernicious anemia			Antibiotics
Rheumatologic disease	RA	10%-30%	Antibody tests are not reliable	IVIg
	SLE			Monoclonal Abs
	SS			
	vasculitis			
Lung disease	Asthma	4%-25%	Radiology Physical examination Biopsy	IVIg
	GLILD			Immunosuppressive agents
Skin disorders	Psoriasis	0%-19%	Physical examination Biopsy Wood's lamp for Vitiligo	IVIg
	Alopecia totalis			Immunomodulatory therapies
	Lichen planus			(topically or systematically)
	Vitiligo			
	Granulomas			

#### 4.1. Hematological diseases

Autoimmune cytopenia as the most common autoimmunity disorder in CVID patients, accounts for up to 25% of CVID-associated autoimmune complications (84, 85). It has been seen in three forms including ITP, AIHA and autoimmune neutropenia (86, 87). USIDNET registry investigated 990 CVID patients and reported autoimmune cytopenia (10.2%), ITP (7.4%), AIHA (4.5%) and autoimmune neutropenia (1%)(88). Interestingly, CVID patients with autoimmune cytopenia had a higher risk for other non-infectious complications, including granulomatous and lymphoproliferative diseases (88). Splenomegaly may be associated with enlarged liver or even abdominal lymphadenopathy. It demonstrates a histologic phenotype of granulomatous reaction in 6 % of cases, and is found occasionally in the patients; however, its pathophysiological link still remains unknown(8, 45, 89). ITP or AIHA may occur as

the first episode of CVID even before definite diagnosis of disease (90).

Autoimmune cytopenia is diagnosed based on abnormal complete blood counts (CBC). Bone marrow biopsy is required when more than 1 cell lineage is disturbed. It helps physicians to differentiate autoimmune cytopenia from bone marrow failure or malignancy (16, 91, 92). The laboratory evidences of hemolysis including increased lactate dehydrogenase and indirect bilirubin levels, reticulocytosis and low levels of haptoglobin associated with a positive direct Coombs test and utilized for diagnosis of AIHA. Given the variability of laboratory testing approaches, usage of anti-platelet or anti-neutrophil antibodies is controversial (93, 94).

Immunosuppressive agents especially oral or intravenous corticosteroids (usually methylprednisolone) are considered as first-line treatment for most autoimmune disorders in CVID patients. Some other similar agents including azathioprine and cyclo-

phosphamide may also be used (95, 96). These kinds of treatment are often beneficial but the relevant increased risk of infections should be considered. Intravenous Immunoglobulin (IVIg) is applied for concurrent management of autoimmunity and immunodeficiency, because of therapeutic effects on ITP and AIHA accompanied by lower incidence of pneumonia in CVID patients (95, 97). Much more effective treatment is the anti-CD20 monoclonal antibody (rituximab) depleting autoreactive B cells as the second-line treatment (7, 98). Recombinant granulocyte colony stimulating factor (G-CSF) is also practical especially in neutropenia cases (3). In refractory cases especially for ITP, splenectomy is considered as the last treatment approach although it must be administered cautiously by physicians because of susceptibility to postoperative infections and sepsis with encapsulated organisms (99, 100).

#### 4.2. Gastrointestinal diseases

Gastrointestinal disorders involve 10 %-12% of CVID patients. These disorders are observed in small intestine or colons, liver and even stomach (93, 101). Intestinal inflammations usually reveals histological patterns resembling conditions like graft-versus-host disease, lymphoid hyperplasia and villous atrophy, that are seen in classic celiac (102). Some features of this celiac-like enteropathy include lymphoid aggregates, intraepithelial lymphocytosis and crypt distortion in small bowel (103). A non-specific inflammation, villous blunting and occasionally granulomas manifest an inflammatory bowel disease (IBD)-like disorder in large intestine. However, decrease or lack of plasma cells and high numbers of CD8<sup>+</sup> T cell infiltrating in the intestinal lamina propria are characteristic features in IBD-like diseases in CVID patients (102, 104). Moreover, increased production of IL-12 and IFN $\gamma$  (instead of IL-23 and IL-17) in lamina propria of CVID patients has been reported (105). These complications often cause severe malabsorption, abdominal pain, diarrhea and weight loss which are commonly due to infectious organisms like

Salmonella species, Giardia lamblia, Campylobacter jejuni, etc (102, 106). The diagnosis is based on laboratory evaluation of inflammatory markers associated with the lack of anti-gliadin antibodies (AGA), anti-tissue transglutaminase antibodies (AtTGA) and anti-endomysial antibodies (EMA). Endoscopy with biopsy of the intestinal mucosa and radiologic imaging are also practical (7, 93). Low-dose corticosteroids are useful even though because of significant risk of infections, higher doses should be avoided. Oral budesonide, and other immunosuppressive agents as azathioprine (AZA) and 6-mercaptopurine (6-MP) are administered in severe cases (107, 108). Unlike autoimmune cytopenia, IVIg is not helpful to ameliorate the IBD-like disease (109). Antibiotics are also prescribed even in the absence of pathogenic organisms. Pernicious anemia, without detectable anti-parietal cell antibodies may occur in 1% to 9% of CVID patients due to atrophic or autoimmune gastritis. Vitamin B12 replacement associated with periodic monitoring for Helicobacter pylori and malignant changes are advisable (110, 111). Autoimmune hepatitis (AIH) is developed in the absence of viral infections or drugs and may eventuate to ascites, cirrhosis and hepatocellular carcinoma. Primary sclerosing cholangitis, primary biliary cirrhosis, portal hypertension and nodular regenerative hyperplasia (NRH) are other liver-related disorders (112). Persistently raised blood alkaline phosphatase levels and mild to moderate periportal lymphocyte infiltration and cholestasis in liver biopsy are characteristic findings (13, 113).

#### 4.3. Rheumatologic diseases

Giannouli et al. in 2004 (114) and Swierkot et al. in 2006 (115) reported that aseptic polyarticular arthritis that resembles rheumatoid arthritis has been observed in 10-30% of CVID patients. Gutierrez et al. reported that (116) the most common rheumatologic manifestation was inflammatory arthritis seen in 35% of CVID patients with rheumatologic disease, which is in line with

previous studies that also describe arthritis as the most common rheumatologic complication in patients with CVID (11, 117). Azizi et al. recently reported that the prevalence of rheumatologic disorders was 10.1% with a higher frequency in women than men (62). Most common rheumatologic manifestations in this cohort were juvenile idiopathic arthritis (JIA) and adult rheumatoid arthritis (RA) followed by juvenile spondyloarthritis (JSpA) and undifferentiated inflammatory arthritis (UIA) (62). Histological abnormalities of the synovial membrane usually differ from those seen in patients with typical form of rheumatoid arthritis (118). Since diagnosis of rheumatoid arthritis is difficult in CVID patients, as serological diagnosis is not reliable and other causes of arthropathy should be excluded namely (119), presence of human leukocyte antigen (HLA) DRB1\*01 antigens seem to be helpful in early rheumatoid arthritis diagnosis (115).

In Gutierrez et al. cohort study (116), SLE and SS, two autoantibody-associated diseases, were among the most common manifestations (with 15.6% and 21.5% of CVID patients with rheumatologic disease respectively), reaffirming that autoantibody-associated disorders may occur even in the setting of deficient immunoglobulin production. They also suggested that since autoantibody profiles are not routinely tested in CVID patients, this observation raises the question of whether CVID patients retain the ability to produce pathogenic autoantibodies. Also, several types of vasculitis were reported in 17.6% of subjects and 11.8% more had other rheumatologic disorders including mixed connective tissue disease, undifferentiated connective tissue disease, Behcet's syndrome, rheumatic fever, and chronic nonbacterial osteomyelitis. Of note, all major autoantibody-associated disorders (e.g. inflammatory arthritis, SLE, Sjogren's syndrome) had a strong female predominance as it is seen in rheumatologic disorders not associated with CVID (116). According to Gutierrez et al. report (116), CVID-associated rheumatologic diseases overlap

with other inflammatory CVID complications in about one-third of the patients, including organ-specific autoimmunity like optic neuritis, uveitis, IBD and autoimmune cytopenias.

#### 4.4. Pulmonary disease

The incidence of asthma has been reported to be between 4% and 15% in children with CVID (120-122). The manifestation of asthma symptoms are delay in CVID patients due to masking the underlying symptoms of immunodeficiency, hence any patient presenting with a chronic or recurrent bronchitis with wheeze should be assumed to have an antibody defect until proven otherwise (123). Such patients must have a full blood count and antibody levels (IgG, IgA and IgM) measured as a minimum, prior to any escalation of asthma medications (124).

Interstitial lung disease in CVID is a potentially devastating outcome, and reported in up to 25% of case series (125). Radiographic abnormalities and surgical biopsy are features of patients with lymphoid interstitial pneumonia, granulomatous lung disease, and lymphoid hyperplasia, which have now been grouped under granulocyte-lymphocytic interstitial lung disease (GLILD) (125, 126). These complications are observed in CVID and CVID-like disorders. These complications are frequently presented with nonspecific symptoms such as cough and dyspnea, and may be mistaken for other forms of interstitial lung disease or granulomatous disease, if underlying CVID is not known or suspected (127). They have a more progressive course and are at high risk for early mortality (125).

Immunoglobulin replacement therapy is the first therapy for these patients (127). The optimal management of patients with GLILD is unclear. However, different treatment strategies for the management of interstitial lung disease have been utilized and include corticosteroids, steroid-sparing immunomodulation and newer biologics, and combination chemotherapy (127-129). Corticosteroids are used most commonly with a general improvement in symptoms, although most of these are anecdotal



reports. Immunosuppressant agents such as azathioprine, rituximab, cyclosporine and methotrexate have been used as steroid sparing agents with variable effects and should be used in consultation with immunologists (129-131).

#### 4.5. Skin disorders

Skin manifestations are commonly observed in PIDs, but have been less reported in CVID patients. Reports of dermatological involvements in CVID including psoriasis, alopecia totalis, lichen planus, and vitiligo have been identified in CVID patients (9, 65, 132).

Gualdi et al. (133) reported that psoriasis had a prevalence of 19.14% among CVID patients. Megna et al. (132) identified 22.4% of CVID patients with psoriasis, as positive family history for psoriasis was observed in 38.5% of them, plaque psoriasis represented the most common psoriasis form in CVID patients. Almost all patients presented a mild form of the dermatosis; which could be due to the immune-modulatory effects of immunoglobulin therapy (134). Indeed, several cases of psoriasis resolution have been reported after immunoglobulin treatment (135).

Granulomas are more frequently found in lungs and lymphoid tissue, but they can also be found in the skin (136), where these may be the presenting clinical manifestations of CVID. Routine dermatological evaluation will allow for timely diagnosis, including biopsy and treatment. The general approach to treatment includes topical or systematic immunomodulatory therapies as would be prescribed for immunocompetent patients (93).

#### Conclusion

Concurrent autoimmunity and immunodeficiency are related to numerous dysregulations in immune molecules and pathways. The precise mechanisms of autoimmunity in CVID are yet unknown and require more investigations. However, it has been demonstrated that CD21<sup>low</sup> B cells expansion plays a significant role in the manifestation of autoimmunity in CVID patients, although the

exact mechanism is still obscure. Moreover, it has been shown that high incidence of infections in CVID leads to chronic stimulation of CD21<sup>low</sup> B cells and may form autoreactive clones. Despite the widespread and relatively successful usage of IVIG, autoimmune or inflammatory disorders in PID patients are still challenging because of difficult treatment. Conventional immunosuppressive treatment approaches for autoimmune manifestations can be perilous for these immunodeficient patients. Exploration of autoimmune disorders and their pathogenesis has been facilitated using the genetic and molecular assays. These methods can help us to find better diagnosis approaches and even more effective treatment for these complications. Hence, early diagnosis of CVID and also appropriate treatment of CVID patients with autoimmunity are critical issues that should be considered in these patients.

#### Conflict of interest

The authors declare no conflicts of interests in regard with this study.

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